REMARKS

Claims 65-144 and 146-157 are now pending in the case, claim 145 having been canceled and new claims 148-157 added by the present amendment. The amendment to claim 65 is supported throughout the specification, e.g., at page 5, line 6. The amendments to claims 84, 146 and 147 are generally supported throughout the specification and particularly in Examples 2, 3, 6 and 7 of the specification, which disclose sterilization of budesonide compositions containing viable microorganisms. See, e.g., page 13, lines 5-6. New claims 148-157 are supported by the disclosure, e.g., at page 4, lines 28-29, and at page 3, lines 1-2. No new matter has been added.

The paragraph on page 1 setting forth the priority information has been amended to reflect the correct information. A Petition to Accept Unintentionally Delayed Benefit Claim is submitted herewith.

According to the Office action mailed November 1, 2005 (the "present Office action"), claims 65-147 stand rejected on one or more grounds. These are discussed below.

35 U.S.C. § 112, first paragraph

Claims 145-147 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 145 has been canceled, and the objected-to language in each of claims 146 and 147 has been deleted by the above amendments to these claims. Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 112, second paragraph

Claims 145-147 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. The rejection of claim 145 is rendered moot by the cancellation of this claim. The language in claim 146 to which the Examiner objects has been deleted from this claim. As the Office action provided no reason for rejecting claim 147 under 112, second paragraph, Applicants are at a loss as to how to respond regarding this claim, and can only assume that claim 147 was included in the rejection in error. Withdrawal of the rejection for all claims is therefore requested.

35 U.S.C. § 103(a)

The Office action mailed November 1, 2005 (the "present Office action") rejected claims 65-70, 73-80, and 84-93 under 35 U.S.C. § 103(a) as allegedly obvious over Jakupovic et al. (WO 96/32095) in view of Rubinfeld et al. (US Patent No. 5,824,668) and Ansel et al. (Pharmaceutical Dosage Forms and Drug Delivery Systems, 1995), for reasons set forth in a previous Office action mailed February 23, 2005 (the "prior Office action"). The present Office action also rejected those claims as well as claims 145-147 as allegedly obvious over Jakupovic in view of PT-69652 (newly cited) and Rubinfeld. All of these rejections, as well as further rejections of the remaining dependent claims based on additional prior art [Radhakrishnan et al. (US Patent No. 5,192,528), Helzner (WO 97/01341), Guy et al. (US Patent No. 5,540,930) and/or Brattsand et al. (US Patent No. 3,992,534)], are premised on the theory that it would have been obvious to produce a sterilized budesonide product that meets the criteria of the claims by employing either of two sterilization processes: (1) filtration of a budesonide solution followed by isolation of powder particles under sterile conditions, or (2) treatment of budesonide powder with ethylene oxide gas (EO). The present Office action also rejects claim 147 as allegedly obvious over Jakupovic combined with Bussey et al. (J. Parenter. Sci. Tech., 1983), on the theory that it would have been obvious to produce the sterile composition of claim 147 by ^{60}Co irradiation.

Applicants disagree with all of these obviousness theories, and have amended some of the claims to make the nonobviousness of the claims even clearer. Each of the supposedly obvious ways to produce sterilized budesonide is discussed below.

Sterilization by filtration (citing Jakupovic, Rubinfeld and Ansel)

The Examiner noted in the prior Office action that Jakupovic discloses a process for generating crystalline budesonide that includes a step of passing a budesonide solution through a filter. Jakupovic does this as a means to introduce the solution into an "anti-solvent" that causes the budesonide to precipitate out as crystalline particles of a desired size. In the Examiner's view, it would have been obvious to use a filter pore size substantially smaller than the low end of the 10-160 micron range preferred by Jakupovic (e.g., approximately 0.2 microns as disclosed by Ansel and Rubinfeld) in order to remove bacteria from the budesonide solution and ultimately produce a sterile budesonide powder. Even though the Examiner agrees that such a pore size

would "probably" make the Jakupovic process too slow to be widely practical (present Office action at page 5, last two lines), she dismisses this clear disincentive to modify Jakupovic by pointing out that the claims are not drawn to a process. Applicants do not understand this reasoning. The Examiner is relying on the supposed obviousness of a hypothetical process that no one in the prior art had ever attempted (or even proposed), in order to find the claimed composition obvious. If (as the Examiner has agreed) one of ordinary skill would not have considered the Jakupovic process with a 0.2 micron filter to be a practical one to try, then it could not have been obvious to produce a sterilized product in this manner. If it would not have been obvious to make the filter-sterilized product, then the filter-sterilized product itself can't be obvious either. The fact that the claims are not drawn to a process does not change the obviousness analysis.

Similarly, the Examiner dismisses Applicants' discussion in the prior response (filed August 22, 2005) of possible problems with filtration sterilization, saying at page 6 of the present Office action, "The fact that one process may be more cumbersome than another may be persuasive in prosecuting a process claim, but the claims are not drawn to a process." Since the question of whether a given product would have been obvious to make is necessarily linked to the question of whether it would have been obvious to carry out the process required to make it, Applicants do not understand the basis for the Examiner's conclusion. If one of ordinary skill would have considered the hypothetical filtration process to be too cumbersome, he/she would not have bothered to try it, and the product would never have been made. Furthermore, many of the issues raised by Applicants in the prior response address whether the significant modification of the Jakupovic process proposed by the Examiner would even work for the purpose intended by Jakupovic—i.e., production of particles of crystalline budesonide of a desired size by direct precipitation in anti-solvent, without the need to use micronization to re-size them. The Examiner has provided no evidence or reasoning to contradict Applicants' quite sensible arguments.

Although the above arguments are more than adequate to rebut the Examiner's prima facie case, Applicants have in fact also amended the claims to provide even more distinctions over the art, in an attempt to move this prosecution along more quickly. Independent claim 65 has been amended to specify that the powder composition was "micronized". Micronization is a

typical means of reducing particle size. Jakupovic sought a technique that could produce particles of the desired size while avoiding the need for micronization, since, according to Jakupovic (see carryover paragraph of pages 1-2), micronization can alter the crystalline structure and physical properties of powder particles in undesirable ways. The Jakupovic process of generating uniform particles of crystalline budesonide is intended, according to Jakupovic at page 3, lines 7-10, and page 4, lines 14-19, to produce crystalline particles of the proper size by direct precipitation from solution, thereby entirely avoiding the need for micronization. Thus, it cannot have been obvious to produce a micronized composition using any process derived from Jakupovic. In fact, Jakupovic taught away from making such a micronized composition. Furthermore, according to Jakupovic at pages 1-2, a micronized composition is structurally distinct from a composition that has not been micronized. Accordingly, amended claim 65 and its dependents cannot be considered to be "obvious" in view of Jakupovic's teachings, taken alone or in combination with Ansel or Rubinfeld or any of the other cited references.

Independent claim 84 has been amended to require that the sterilized powder composition have been produced by sterilization of "viable-microorganism-containing particles" of budesonide (or an ester, acetal or salt thereof). Independent claims 146 and 147 also now recite similar language. These limitations ensure that there is a clear structural difference between the claimed sterilized compositions and the hypothetical filter-sterilized composition the Examiner supposes would have been "obvious" in view of Jakupovic, Rubinfeld, and Ansel. Any mode of sterilization of budesonide *particles* (i.e., not a budesonide solution) containing viable microorganisms will produce a composition of budesonide particles *that necessarily contains killed microorganisms*. In contrast, filter sterilization of a budesonide solution would, in theory, *remove* all microorganisms, dead or alive. The Examiner has acknowledged that this is indeed a valid structural distinction between a filter-sterilized product and a product sterilized by other means (present Office action at page 6, lines 7-9). Thus, amended claims 84, 146, and 147, and all claims dependent thereon, are distinguished over the Jakupovic, Rubinfeld, and Ansel "filter sterilization" combination of references.

Sterilization by ethylene oxide (EO) treatment (citing Jakupovic, Rubinfeld and Ansel or Jakupovic, Rubinfeld and PT-69652)

The Examiner continues to cite Rubinfeld and Ansel for their teachings that steroid compounds may be sterilized using EO (pages 4-5 of the present Office action), combining that teaching with Jakupovic's teaching of unsterilized budesonide particles. In a separate rejection set out at pages 7-8 of the present Office action, the combination of Rubinfeld with PT-69652 and Jakupovic is newly cited for the same purpose. Applicants traverse both rejections.

Rubinfeld mentions, without elaboration, at col. 14, lines 16-13, that powder compositions can be sterilized with EO. Although Applicants' response filed August 22, 2005, pointed out that two different 1983 references (Bussey et al., J. Parenteral Science and Technology 37:51-55, 1983; and Kane et al., J. Pharmaceutical Sciences 72:30-35, 1983) and a third document (the Purwar patent, US Patent No. 6,066,292) filed shortly after the priority date of the present application all raised serious concerns about use of EO for sterilizing drugs (concerns that were NOT addressed by Rubinfeld), the Examiner brushes these concerns off as though they were irrelevant. Regarding the Kane et al. reference, the Examiner inexplicably says that it was "published after Applicant's filing date", which clearly is not true, and that it discloses that strict limits were proposed by the FDA "several years after Applicant's filing date," again clearly not true, given the 1983 publication date of Kane et al.[1] Applicants pointed out that the Rubinfeld reference does nothing to counteract these teachings in the art; to that, the Examiner responds that "the emphasis of Rubinfeld is not a process of sterilization, per se, so there is no expectation that the reference would discuss what is known in the art about this process." While Applicants agree that Rubinfeld was not focused on sterilization processes and would not be expected to discuss them in detail, Applicants strenuously disagree with the implication that this lack of discussion can be taken to be evidence that EO sterilization was a generally accepted method for sterilizing new pharmaceuticals at the time of the invention. Rubinfeld may simply have chosen not to bother to discuss the drawbacks. The Kane et al. and Bussey et al. references are clear evidence that by 1983 the EO method, though "grandfathered in" for some drugs, was

[1] In fact, the FDA proposed the limits in 1979; to Applicants' knowledge, the proposed rule may have been rescinded, but not until well after Applicants' 1997 priority date. This is discussed further below.

fast falling out of favor for those not grandfathered in, because of serious safety issues. The Purwar reference puts it into perspective:

> **Most of the products sterilized by [EO] were introduced in the market decades ago and probably would not be allowed to be introduced today due to present day's stringent regulatory requirement for almost zero ethylene oxide residue."** (col.1, lines 57-61)

Rather than recognize the probative value of this statement, however, the Examiner dismisses it "because the emphasis of PURWAR *is* the description of a new process of sterilization, as an alternative to the process using EO. As such, PURWAR would clearly be motivated to explicitly accentuate the disadvantages of alternative processes." (emphasis in the original) In doing so, the Examiner seems to be taking the rather curious position that a reference that is not focused explicitly on methods of sterilization and that does not discuss their disadvantages (i.e., Rubinfeld) is, by definition, more probative regarding their disadvantages (or lack of same) than is a reference that is focused explicitly on methods of sterilization and does discuss some disadvantages (i.e., Purwar). Applicants ask the Examiner to reconsider that position.

As further evidence that use of EO to sterilize drugs (other than certain "grandfathered" drugs) had fallen out of favor by 1997, Applicants submit two further documents. The first (Ref. AJ on the enclosed form PTO-1449) is an excerpt from "Guidelines-Medical Products for Human Use," published by the European Agency for the Evaluation of Medicinal Products (EMEA, the European equivalent of the U.S. Food & Drug Administration) to assist those applying for marketing authorization in the European Union. The excerpt includes a section entitled "Manufacture of the Finished Dosage Form" (adopted in 1995 and entered into force in 1996) and a section entitled "Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products" (adopted in 1993 and entered into force in 1994). According to the latter section at page 21,

> **In view of the known positive potential of ethylene oxide for genotoxic carcinogenicity, it is recommended that use is acceptable only when pharmaceutically absolutely necessary, and then at a limit of 1 ppm. This limit is based on the current limit of detection for ethylene oxide.**
>
> **Any deviation upwards from this limit must be justified and defended, taking into account the clinical risk/benefit assessment for the particular products under consideration.**

* * *

Ethylene oxide sterilisation should be used only where safer alternatives cannot be used.

This strongly teaches away from experimenting with use of EO to sterilize pharmaceutical products.

The U.S. Food & Drug Administration (FDA) has, insofar as Applicants are aware, not issued such a clear-cut numerical limit on permissible EO residues in drug preparations in general or inhalable powders in particular. A proposed rule published by the FDA in 1978 (Ref. AI on the enclosed form PTO-1449) discusses the dangers of EO and proposes maximum EO residue limits for certain categories of drugs and devices. The drug categories listed on page 27482, middle column, do not include inhalable powders. The document says that "manufacturers should attempt to achieve even lower levels" and that further toxicity experiments were underway (page 27480, middle column). It is Applicants' understanding that these proposed rules languished as "proposed rules" for several years, and were withdrawn around 2000. They are described here merely as further evidence that as early as 1978, the FDA regarded EO as dangerous and recommended that it be avoided or minimized.

More to the point is another newly submitted document (Ref. AL on the enclosed form PTO-1449), a printout from the FDA website (www.fda.gov/ora/inspect_ref/igs/iglist.html) printed on May 30, 2006, and entitled "Guide to Inspection of Sterile Drug Substance Manufacturers." It apparently was originally published in July 1994.[2] On page 6 of 7, in the section headed "IX. Terminal Sterilization", the Guide to Inspection discusses sterilization with EO:

> **With regard to ethylene oxide, a substantial part of the sterile bulk drug industry has discontinued the use of ethylene oxide as a "sterilizing" agent. Because of employee safety considerations, ethylene oxide residues in product and the inability to validate ethylene oxide sterilization, its use is on the decline. As a primary means of sterilization, its utilization is questionable because of lack of assurance of penetration into the crystal core of a sterile powder.**

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[2] Attached behind the seven first pages is a table of contents from the same website. Page 2 of the table of contents includes (under the "Drugs" subheading) a link to "Sterile Drug Substance Manufacturers" together with the date "7/94", indicating that the "Guide to Inspection of Sterile Drug Substance Manufacturers" was published in July 1994.

Ethylene oxide has also been utilized in the treatment of sterile powders. Its principal use has been for surface sterilization of powders as a precaution against potential microbiological contamination of the sterile powder during aseptic handling.

Taken together, these newly submitted documents make it very clear that the regulatory authorities in both the U.S. and Europe had concluded, well before 1997, that use of EO to sterilize drug products was to be avoided if possible. The regulatory authorities raise employee safety concerns, concerns about EO residues in the product, and concerns about whether EO can adequately kill microorganisms encased in the crystal core of a drug particle to support their position that EO is not a desirable means to sterilize drugs.

The point about incomplete sterilization when EO is used is further elaborated by Mullican and Hoffman, Applied Microbiology 16:1110-1113, 1968 (submitted herewith as Ref. AM on the enclosed form PTO-1449). Mullican and Hoffman showed that, while treatment with EO was generally effective at sterilizing the surfaces of NaCl crystals contaminated with bacterial spores, it was entirely incapable of decreasing the count of viable bacterial spores encased inside intact crystals of either NaCl or glycine, even when the EO treatment was continued for 48 hours. Only when the crystals were partially or completely dissolved by exposure to high humidity did the EO treatment become effective for reducing the count of what had been the encased viable spores[3] (page 1112, carryover paragraph of col.1-2). This makes sense, as EO would need to come into direct contact with the microorganism in order to have an effect on it, and presumably could not contact anything that is encased in a solid, non-porous substance. Since budesonide does not dissolve appreciably in water (and anyway dissolving what is supposed to be a powdered drug in the course of sterilizing it would not be acceptable), treatment of budesonide particles with EO would not be expected to result in a satisfactorily sterilized product.

We turn now to the PT-69652 reference newly cited in the present Office action. It purports to teach a method for EO sterilization of micronized steroid powders. In fact, this

[3] In dramatic contrast, Tables 1 and 2 on page 1112 of this publication show that dry heat treatment (125°C) left no encased spores surviving in NaCl or glycine crystals after 16 hours or 24 hours, respectively.

reference would not convince one of ordinary skill that the disclosed method of sterilization with EO is worth trying, for at least the three reasons enumerated below.

1. *There is no indication anywhere in the reference that the described method actually successfully killed any microorganisms, much less achieved what could be termed a "sterilized" product.* Though the reference takes pains to describe in detail an experiment with EO (see pages 6-11 of the PT-69652 English translation), the lack of any disclosure of whether it actually worked is striking. No data pertaining to the degree of sterilization achieved (whether in the "celite packages containing a biological indicator" or in the steroid samples themselves) is provided. In view of the Mullican and Hoffman EO experiments discussed above, which teach away from use of EO to sterilize powder particles, it would in fact be surprising if the PT-69652 technique actually managed to kill microorganisms encased in the steroid particles. Accordingly, one of ordinary skill reading PT-69652 would have no reason to think that the disclosed technique actually works and so is worth trying.

2. *PT-69652 does not make the case that residual EO can be effectively eliminated from the steroid product using the disclosed technique.* The reference purports to describe a degassification process whereby essentially all residual EO is eliminated from the product, but in fact the evidence supporting this assertion is inconclusive at best. For example, look closely at the technique employed by the PT-69652 patent to measure residual EO. This technique relies on what is reported to be the equivalent absorbance of 1 ml of a "standard potassium chromate solution" and 10 mg of EO (an equivalence stated at page 8, lines 20-21, and reiterated at page 10, line 10, of the English translation). For reasons that are not made clear, the equation on page 11 introduces a thousand-fold difference in that equivalence, stating that 1 ml = 10 **µg** instead of 10 **mg**. (The same units are used in the original Portuguese text, so this is not a typographical error introduced in the translation.) This is just one source of confusion. A second is in the apparent failure to take into account the 7.5-fold dilution of the sample described at page 10, lines 12-18, where just 2 ml of the 15 ml EO solution was used to obtain an absorbance reading. Then there is the inherent inaccuracy of any measurement made by extrapolating from a calibration curve to a region far below the lowest datapoint on the curve.

As disclosed on page 10, a standard calibration line was made using samples containing different amounts of the standard potassium chromate solution (from 1 to 6 ml), and plotting those amounts against their absorbance at 412 nm. Thus, the lowest datapoint on the calibration line corresponded to 1 ml of the standard potassium chromate solution, supposedly the equivalent of 10 mg of EO, if one believes the statement at page 8, line 20, that is repeated at page 10, line 10, or possibly the equivalent of 10 μg EO, if one instead chooses to believe the statement at page 11, both of which are far higher than the 1 ppm maximum permitted by the EMEA as discussed above. Also, PT-69652 recognizes that the error inherent in the technique will vary with different steroids due to varying levels of "interference" (see pages 7-8); for 9-alphafluoroprednisolone ("9-fluoro") an overall error of 14% was reported (page 9, lines 13-16). PT-69652 goes on to say that "the final error would not be more than a few p.p.m." Given these considerations, one of ordinary skill would not trust the PT-69652 patent's assertions in the final paragraph on page 9 that the amount of EO remaining in the sterilized 9-fluoro product was "0 p.p.m" or "perfectly negligible." This reference simply does not provide evidence that EO sterilization can be carried out in a way that produces a product with an acceptably low level of residual EO.

3. *PT-69652 does not address the issue of whether EO forms adducts with, and thereby irreversibly damages, an unacceptably high proportion of steroid molecules during the sterilization process.* EO is a highly reactive alkylating agent that can form adducts with nucleophilic functional groups on drug molecules (see, e.g., the Khorshidi abstract discussed on page 19 of Applicants' response filed August 22, 2005). Given that even the presumably low levels of EO remaining in a container after EO sterilization of the container can produce such adducts with the drug that is subsequently packaged in the container (as explained by Khorshidi), one would expect the much higher level of EO in contact with the drug during the PT-69652 sterilization process to result in alteration of any drug (such as budesonide) that has nucleophilic functional groups. That this was well known before the present application's priority date is evidenced by the comment in the Ansel reference explaining that when EO is used to sterilize drugs, "**tests [are] performed to assure of the absence of chemical reaction or other deleterious effects on the drug substance**" (page 298, left column). Ansel's comment makes it

clear that one of ordinary skill would not consider using any EO sterilization technique without assurance that the drug would not be adversely affected. Neither PT-69652 nor any other reference cited by the Examiner provides such assurance.

Applicants have described three independent reasons that one of ordinary skill would have found the PT-69652 reference to be unconvincing. Objective evidence that this is still the case can be found in US 2005/0201888 (Ref. AB on the enclosed Form PTO-1449), which discusses PT-69652 in paragraph [0004] and then says in paragraph [0005]:

> **However, ethylene oxide is toxic and when it is used to sterilize glucocorticosteroids it has been found that the residual amounts of the ethylene oxide contravene pharmaceutical guidelines, which require very low levels of residual ethylene oxide. Accordingly this method has been found to be unsuitable for producing therapeutically acceptable glucocorticosteroids and formulations thereof.**

It is clear that one of ordinary skill who was aware of all of the cited art in 1997 would not have considered using EO to be a viable method of sterilizing budesonide. If it was not obvious to try sterilizing budesonide with EO, the product of such a sterilization method also cannot be considered obvious.

The above evidence establishes that one of ordinary skill in the art would not have considered using EO to sterilize budesonide particles at the priority date, and so goes to the nonobviousness of all of the present claims in view of the EO prior art. Applicants point out that there are further reasons that claims 88, 146 and 147, and all claims dependent thereon, are patentably non-obvious over the cited art relating to sterilization with EO. Each of these claims is now limited to a budesonide composition that was produced by heat sterilization of a powder (or particle) composition containing "viable microorganisms". EO is an alkylating agent that kills microorganisms by chemically reacting with cellular proteins, forming adducts (see page 246, right column, of Prescott et al., *Microbiology*, Wm.C.Brown Publishers, Dubuque, IA, 1990; Ref. AN on the enclosed Form PTO-1449). (It may also form adducts with the drug itself, if the drug molecule contains nucleophilic functional groups such as those found in budesonide. See the Khorshidi abstract discussed on page 19 of Applicants' previous response filed August 22, 2005.) In contrast, heat treatment kills microorganisms by denaturation of protein or

by dehydration of the cell followed by oxidation (Ansel, page 294, right column). It is clear that the product encompassed by claims 88, 146, and 147 would necessarily contain heat-killed microorganisms that would be structurally distinct from the killed microorganisms present in a budesonide powder treated by a means other than heat, including but not limited to EO treatment.

Sterilization by irradiation with ^{60}Co (citing Jakupovic and Bussey)

The Examiner rejected claim 147 as claiming a product-by-process that she theorizes could have been produced by sterilizing with ^{60}Co, and thus allegedly obvious in view of Jakupovic combined with Bussey. As acknowledged in the present Office action, Applicants remarked in the previous response that the claimed powder necessarily lacks the characteristics of a product that has been previously sterilized by irradiation, i.e., irradiation by-products present. The Examiner asserts "This limitation would only preclude the use of irradiation if such by-products could only be generated by irradiation," but provides no evidence or reasoning to support the theory that such by-products could exist in the absence of irradiation. Applicants believe that the burden is on the Examiner to base obviousness rejections on something more than a purely hypothetical guess. Furthermore, the rejection completely ignores the second, independent basis for nonobviousness of this claim set forth on pages 20-21 of Applicants' previous response, reiterated here for the Examiner's convenience:

> Furthermore, the claimed composition will contain heat-killed bacteria, regardless of what further hypothetical manipulations the composition undergoes after the specified heat-sterilization step. Thus, regardless of how obvious or non-obvious it would have been to try sterilizing a budesonide powder by an alternative technique such as irradiation, the product of that alternative technique would not have produced a sterile composition identical in all respects to the one claimed.

The claim has been amended to replace the term "unsterilized powder" with a limitation requiring the presence of "viable microorganisms" in the composition that is subjected to the heat treatment step, but the concept is the same as argued previously. This limitation guarantees that heat-killed microorganisms are present in the final product. Although irradiation also kills microorganisms, the structural changes produced in microorganisms by irradiation are not the same as those resulting from heat (compare Ansel's description of heat-killed microorganisms at

page 294 with his description of radiation-killed microorganisms at page 298). One would not expect to find heat-killed microorganisms, or anything structurally identical thereto, in a product that has not been sterilized by heat. Accordingly, the claimed product is not identical to a product that was never heat-sterilized.

Withdrawal of the rejections for obviousness over the filter-sterilization art (Jakupovic/Rubinfeld/Ansel), the EO-sterilization art (Jakupovic/Rubinfeld/Ansel and Jakupovic/PT-69652/Rubinfeld), and the irradiation art (Jakupovic/Bussey) is therefore respectfully requested.

Double Patenting Rejections

Claims 94-102, 105, 107-109, 136-138, and 142-144 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 12, or 22 of US Patent No. 6,686,346, in view of Rubinfeld and Ansel, repeating the rejection made in the prior Office Action. The prior Office Action states that claims 1, 12, and 22 of the '346 patent recite a suspension (or administration of suspension) comprising budesonide suspended in an aqueous medium. It further states that though claims 1, 12, and 22 of the '346 patent do not require the suspension to be sterile, it would be obvious to prepare the suspension in sterile form and that one of ordinary skill would reasonably expect success in preparing a sterile composition using the teachings of Rubinfeld and Ansel.

Applicants respectfully disagree. As discussed at length above, neither Rubinfeld nor Ansel would have rendered it obvious to produce a sterile or sterilized budesonide composition that meets the criteria of the present independent claims 65 and 84, from which all of the rejected claims depend. The cited claims of the '346 patent do not make up for this deficiency. Accordingly, Applicants respectfully request withdrawal of this rejection.

Claims 94-101, 136-138, and 142-144 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 or 8 of US Patent No. 6,291,445, in view of Rubinfeld and Ansel, repeating the rejection made in the prior Office Action. The prior Office Action states that claims 2 and 8 of the '445 patent recite a

suspension (or administration of suspension) comprising budesonide suspended in an aqueous medium. It further states that though claims 2 and 8 of the '445 patent do not require the suspension to be sterile, it would be obvious to prepare the suspension in sterile form and that one of ordinary skill would reasonably expect success in preparing a sterile composition using the teachings of Rubinfeld and Ansel.

Applicants respectfully disagree. As pointed out above, neither Rubinfeld nor Ansel suggests how to obtain a sterile or sterilized budesonide composition that meets the criteria of the present claims. Combination of these references with the '445 patent does not cure this deficiency. Accordingly, Applicants respectfully request withdrawal of this rejection.

Conclusion

Applicants submit that all claims are allowable; such as action is requested.

Fees in the amount of $400 for excess claim fees and $790 for RCE fee are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 06275-160002.

Respectfully submitted,

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